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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,872	04/25/2001	Antonio J. Grillo-Lopez	P 0280609/2000-30-154A	4921

909 7590 10/20/2004

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/840,872	GRILLO-LOPEZ, ANTONIO J.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 September 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or 2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *56-60 and 62-67*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *PTO-892*

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit: 1642

Re: Grillo-Lopez, A.

Date of priority: 04/25/2000

Response to Amendment

The Amendment filed 09/27/04 in response to the Office Action of 07/26/04 is acknowledged and has been entered.

Claim 61 was cancelled.

Claims 56-60, and 62-67 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 56-60, and 62-67 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,776,456 (Anderson *et al.*) in view of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252) for the reasons of record in the Action mailed 07-26-04 and for the reasons set forth below.

Initially, applicants argue (page 5) that the addition of the Caligiuri reference (which teaches the treatment of CNS lymphomas with anti-Fas antibodies) "does not enable administration of anti-

CD20 antibodies as now claimed". Applicants argue that at the time of filing the instant application a skilled artisan would not have had a reasonable chance of success in practicing the claimed invention. This argument has been considered but is not really well understood by the examiner. Applicants only appear to state an assertion without evidentiary support. Further, it's not clear how this argument is relevant to the current rejection.

Applicants go on to individually describe the teachings of Anderson, Caligiuri, and DeAngelis while summarizing the previous Office Action with regards to intrathecal and intraventricular routes of administration. Applicants further note that the Examiner disagreed with applicants' previous assertions that "known intrathecal administration did not predictably result in elevated levels of administered antibodies in cerebrospinal fluid". Applicants further note (page 6) that Claim 56 is now amended to specify the route of administration as intrathecal or intraventricular and that the combination of the references does not teach, suggest, or motivate intrathecal administration of anti-CD20 antibodies as now claimed. Applicants argue that "the Caliguiri patent does not generally suggest intrathecal administration or any antibody and does not suggest administration of an anti-CD20 antibody". These arguments have been carefully considered but are not found persuasive. While the Caliguiri reference does not specifically teach administration of the claimed anti-CD20 antibodies, one of ordinary skill in the art who reads the Caliguiri reference would understand that primary lymphomas of the CNS are treatable with antibodies- a lesson which is particularly relevant to the teachings of the Anderson patent which also concludes that lymphomas (in general) can be treated with antibodies. Thus, taken together, the references reasonably suggest that: a) either anti-CD20 or anti-Fas antibodies kill

lymphoma cells and b) CNS lymphomas can be successfully treated by intrathecal administration of antibodies.

Applicants further argue (page 6) that one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of Caliguri with an anti-CD20 antibody because "such motivation would not have existed as of the filing date of the instant application because success in performing such method did not reasonably exist". This argument has been considered but is not found persuasive. It is noted that success in broadly treating any B cell lymphoma in a human patient existed well before the filing date of the instant application as the earliest date of the Anderson patent was in 1992. Further, treating a central nervous system lymphoma with antibodies existed in 1996 (Caliguri patent).

Applicants further argue (page 7) that the Caliguiri patent does not include any experimental results showing that anti-Fas antibodies can be administered to a subject via intrathecal injection to thereby achieve antibody levels that are higher in cerebrospinal fluid than in serum. Applicants contend that the absence of this experimental evidence is reason enough to conclude that the skilled artisan would not have concluded that the presently claimed invention could be achieved with any reasonable chance of success. This argument has been considered but is not found persuasive. Every patent is presumed valid (35 U.S.C. 282) which includes the presumption of operability *(Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935). Further, applicants have not provided any affidavits or declarations that specifically refute the operability or enablement of the Caliguiri patent- which must rebut the presumption of operability by a preponderance of the evidence. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). The above is further applicable to applicant's arguments that the examiner has

not cited any reference that demonstrates successful intrathecal administration of antibodies (page 7, 2nd paragraph) as again, applicants have not provided evidence to rebut the presumption of operability as taught by the Caliguiri patent.

Applicants further reiterate their arguments that the Cokgor and Blaney references support the unpredictability of intrathecal administration despite the fact that neither reference refers to intrathecal administration of antibodies. These arguments, having been considered previously, are not found persuasive for the reasons of record.

Applicants further present the Hanssens reference in which the abstract states, "In practice, intrathecal radiation is still under investigation and subject to some limitations and toxicities." However, despite the alleged teaching away, the reference fails to reasonably suggest the inoperability of intrathecal administration of antibodies. In fact, the literature is replete with prior art (as early as 1996) demonstrating therapeutic intrathecal administration of antibodies. For example, see Bergman *et al.* (Int. J. Cancer, 1999, Vol. 82, pp.538-548) and Brown *et al.* (Clin. Cancer Res., June 1996, Vol. 2, No. 6, abstract). Thus, applicants' arguments have not been found persuasive and the rejections are maintained.

Claims 56-60, and 62-67 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,776,456 (Anderson *et al.*) in view of the teachings of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252) for the reasons of record. Applicants reiterate their arguments as set forth above. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

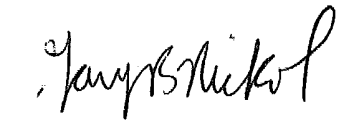
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN



GARY NICKOL
PRIMARY EXAMINER